Remarks

Claims 1-5, 8-18, 22-24, 26-27, 30-32, 72-75 and 80-86 were pending in the application. Applicants thank Examiner Epps-Ford for joining claims 4, 15, 17-18, 22-24, 37, 30-32, and 80-86 in this application. Claims 3-4, 14-15, 24, 26-27, and 80-82 are cancelled without prejudice to prosecution in another application. Claims 87-88 are added. Therefore, claims 1-2, 5, 8-13, 16-18, 22-23, 30-32, 72-75, and 83-88 are now pending.

Claims 1-2, 11-13, 17-18 and 75 were amended herein to clarify that Notch is human Notch-1. Support can be found throughout the specification, for example, page 3, lines 30-32; page 4, lines 4-7; page 5, lines 7-9; and original claims 3 and 14. Claim 75 was also amended to correct a typographical error in the term "concurrently." No amendments made herein were to distinguish prior art, but were instead made to advance prosecution.

Claims 87-88 were added. Support can be found throughout the specification, for example, claims 1, 11, 13, and 16.

No new matter is added by these amendments.

Summary of Telephone Interview

On March 12, 2004, a telephone interview was conducted between Applicants' representative Sheree Lynn Rybak, Ph.D. and Examiner Epps-Ford. During the conversation, the 35 U.S.C. § 112, first paragraph rejections were discussed. In order to obtain claims to the use of the genus of agents that interfere with Notch function, Applicants agreed to amend claim 1 to clarify that Notch-1 refers to human Notch-1. Because Applicants have provided numerous specific species of agents that interfere with human Notch-1 function (such as antibodies and antisense molecules), claims directed to methods of using the genus of agents that interfere with human Notch -1 function, in combination with a differentiation inducing agent, to induce apoptosis, should be allowed.

In addition, Applicants' representative and Examiner Epps-Ford discussed the *in vivo* data that the examiner thought would be minimally required to obtain claims to in vivo methods of use. Examiner Epps-Ford stated that animal data, such as experiments in mice, would be required. Examiner Epps-Ford suggested administering human Notch-1 antisense molecules, in combination with a differentiation agent, and showing the effects on tumor development or regression. Control studies should include the differentiation agent alone, the antisense molecule alone, and neither agent. In addition, Examiner Epps-Ford suggested testing at least 2-3 different antisense molecules, in order to obtain claims to the genus of agents that interfere with human Notch-1 function.

35 U.S.C. § 112, second paragraph

Claim 1 was rejected under 35 U.S.C. § 112, second paragraph, on the ground that the phrase "exposing the cell an agent..." is grammatically incorrect. Applicants thank the examiner for bringing this error to our attention, and have amended the phrase to read "exposing the cell to an agent...." In view of this amendment, Applicants request that this 35 U.S.C. § 112, second paragraph rejection be withdrawn.

35 U.S.C. § 112, first paragraph

Claims 1-5, 8-15, 17-18, 22-24, 26-27, 30-32, 72-75 and 80-86 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that the claims contain subject matter which was not described in the specification in a way that conveyed the inventors had possession of the claimed invention. Applicants respectfully disagree and request reconsideration.

It is asserted that although the specification discloses antisense molecules and antibodies that target Notch-1, the claims are drawn to a broad class of antisense molecules and antibodies that target all forms of Notch. In order to expedite prosecution, claim 1 has been amended to clarify that the agent that interferes with Notch function interferes with human Notch-1 function. Therefore, the claims are now drawn to a method of inducing apoptosis by using a differentiation inducing agent in combination with any member of the genus of agents that interfere with human Notch-1 expression or function.

The genus of agents that interfere with human Notch-1 expression or function was known in the prior art. For example, Austin *et al.* (*Development* 121:3637-50, 1995), Waid and

McLoon (*Development* 125:1059-66, 1998), and Bartlett *et al.* (*Immunol. Cell Biol.* 76:414-8, 1998) (all of which were published before the March 12, 1999 priority date of the present application), disclose specific Notch antisense molecules that were used to inhibit Notch expression. Copies of these articles are enclosed as Exhibits A, B, and C, respectively. Furthermore, although WO 94/07474 (previously cited by the Examiner) does not disclose particular sequences of Notch antisense molecules, that application discloses that Notch antisense molecules can be used to inhibit Notch expression (for example, see pages 31-36). Therefore, unlike the cases cited in the Office action on pages 3-6 in which the structure of the claimed invention was essential for what was claimed, the present invention only requires interfering with Notch expression or activity. Since agents that interfere with Notch expression or activity were known prior to the priority date of the present application, the claims should not be limited to particular examples of such agents.

Therefore, Applicants request that this part of the 35 U.S.C. § 112, first paragraph rejection be withdrawn.

Claims 1-5, 8-16, 26, 30-31, 72-75, 80, 82 and 84-86 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that the claims are only enabled for practicing the method *in vitro*. Although the data in the specification only uses tissue culture cells, Applicants have demonstrated that several Notch-1 antisense and several Notch-1 antibodies, in combination with a differentiation agent, induce apoptosis (see Examples 8-13 of the specification). Since multiple different agents decreased Notch-1 activity, this decreases the unpredictability in this art. Based on these results, one skilled in the art would expect similar results *in vivo*. That is, one of any number of agents that decrease Notch-1 activity, in combination with a differentiation agent, will induce apoptosis of a Notch-1 expressing tumor cell *in vivo*.

Furthermore, as discussed in Chapter 2100 of the MPEP, the Federal Circuit has held that in vitro results can be sufficient to show pharmacological activity. For example, in Cross v. Iizuka, 753 F.2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985), the Federal Circuit concluded that "under appropriate circumstances . . . *in vitro* testing may establish a practical utility for the compound in question." Furthermore, in In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995), the Federal Circuit concluded that FDA approval is not required to find a compound useful. Just as *in vitro* activity is probative of *in vivo* activity for utility purposes, the

in vitro demonstration of activity with multiple agents in the specification would convince one skilled in the art that the method also has *in vivo* activity. The specification is therefore enabling for both *in vitro* and *in vivo* methods.

In view of the *in vitro* results presented in the present application, in combination with rulings from the Federal Circuit which hold that *in vivo* data is not required, Applicants request that this part of the 35 U.S.C. § 112, first paragraph rejection be withdrawn.

If any issues remain before a notice of allowance is issued, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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